protein has either C3b or C4b cofactor activity, comprising adding sequences to the protein conferring binding of the other ligand, either C4b or C3b.

Remarks

Restriction Requirement

Claims 1-34 were restricted into two groups, group I, claims 1-32 and 34, drawn to a protein, a DNA sequence encoding the protein and a method for enhancing C4b or C3b cofactor activity, and claim 33, drawn to a transgenic animal. The claims were also divided into multiple species: complement regulating proteins containing SCR from a second different protein; proteins containing rearranged SCRs; proteins having specific defined amino acid substitutions in the SCRs; and consisting of as few as three SCRs. The claims were also divided into species on the basis of the protein of origin: CR1, DAF, or factor H.

Applicants affirm their election of group I, without traverse. Claim 33 has been cancelled.

Applicants also affirm their election to prosecute claims drawn to the protein as CR1.

Applicants do not affirm their election to prosecute the species where the SCRs include SCRs from a second protein; this is overlapping in scope with applicants' copending application U.S.Serial No. 08/210,266 filed March 18, 1994, which

is a file wrapper continuation of U.S. Serial No. 07/695,514 filed May 3, 1991. This application is being examined in Art Unit 1812, Examiner S. Guest Cermak.

Applicants elect the species of proteins having defined specific amino acid substitutions, with the understanding the generic claims will be examined should the species be found to be allowable. Only the claim which has been restricted out has been cancelled; the remaining claims are left pending in view of the election of species requirement and are treated below as if all claims had been examined.

Objections under 37 C.F.R. §112

The title, specification and the abstract have been amended in response to the Examiner's objections.

The status of the parent application is that it is now abandoned in favor of the continuation application referenced above.

The objection to the drawings is noted; formal drawings will be submitted when there is allowable subject matter.

Rejections under 35 U.S.C. §101 and §112

The specification and claims 1-32, and 34 have been rejected under 37 C.F.R. §101 as lacking utility and under §112,

first paragraph. These rejections are respectfully traversed as applied to the amended claims and in view of the accompanying materials.

The claims are directed to specific modifications of naturally occurring complement inhibitors which are characterized by "SCR"s, short consensus repeats that have biological activity *in vitro* as measured using standard *in vitro* assays. Applicants have used genetic engineering to create new proteins which incorporate one or more SCRs from other proteins having defined activities, having rearranged SCRs, or specific amino acid substitutions. The elected species, those having defined amino acid substitutions of CR1 are clearly demonstrated in the application to have the claimed *in vitro* activities. As demonstrated in the application, the biological activity of these proteins has been determined using standard *in vitro* assays. The basis for the Examiner's rejection appears to be that one skilled in the art could not extrapolate from *in vitro* assays to *in vivo* applicability.

The use of *in vitro* assays to predict *in vivo* activity has been established and used by those in both research and clinically for decades. These assays are no more unpredictable than clotting assays: the same components *in vitro* are those which are involved *in vivo*. Reference to these assays are found throughout textbooks on immunology and hematology as well as

clinical laboratory manuals. Accordingly, one skilled in the art would view the assays used by applicants as predictive of *in vivo* activity.

Moreover, the proteins from which these SCRs are derived have been shown to be active naturally, and the activity correlated with the *in vitro* assays. Both MCP and CR1 have been expressed from recombinant sequences, as they occur naturally and in soluble and modified forms (CR1 has been shortened to as few as four SCRs) and shown to be active *in vitro* and *in vivo*, using an Arthus animal model, which is a standard model for inhibition of complement activity. The activity of the soluble MCP is described in co-pending application U.S. Serial No. 08/203,867; a copy of a Declaration under 37 C.F.R. §1.132 is enclosed to demonstrate *in vivo* activity of a soluble form. The activity of a shortened form of CR1 was reported by Yeh, et al., "Recombinant Soluble Human Complement Receptor Type 1 Inhibits Inflammation in the Reversed Passive Arthus Reaction in Rats" J. Immunol. 146, 250-256 (January 1991), a copy of which is enclosed with this response. The ability of a similar soluble recombinant CR1 to inhibit post-ischemic myocardial inflammation in rats was reported by Weissman, et al., Science 249:146-151 (1990), a copy of which is enclosed. These provide additional evidence that the *in vitro* assays are predictive of *in vivo* activity.

It is respectfully brought to the Examiner's attention that the claims are directed to proteins for inhibiting complement mediated inflammation. The disclosure should be enabling for one of ordinary skill in the art to inhibit inflammation arising from complement activation. It is well known to those in the art which are complement mediated inflammatory conditions. Immunology textbooks abound with such information and the assays are routinely administered in every hospital. Determining an effective dosage is routine.

The material referenced as described in Figures 2A and 2B is described in the application to which this application claims priority; it is for background purposes only, not essential material, and the reference has been deleted. The substitutions demonstrated by Figures 2A and 2B, as well as Figures 3A and 3B, are specifically described in Table 2; the figures are to aid in understanding the rationale behind the substitutions.

Claims 16-18, 23, and 27-30 have been amended to more clearly recite process steps, as objected to by the Examiner.

The Examiner's objection regarding incorporation of essential material is noted; however, the publications are clearly cited by applicants and the DNA sequences encoding the naturally occurring proteins are well known and accessible to any one skilled in the art. It is well established that one need not

disclose that which is known to those skilled in the art; indeed, it is recommended that one only disclose that which is new. One does not have to provide the method for synthesis for a commercially available reagent; one should similarly not have to provide the DNA sequence for every imaginable DNA molecule one might choose to practice the claimed invention.

The claims have been amended in response to the Examiner's objection regarding scope at page 8, by requiring that the claimed proteins specifically bind C3b and/or C4b. With respect to the remark regarding diagnostic applications, it should be noted that intended use is a meaningless limitation in a composition claim (i.e., as when the intended use is either diagnostic or therapeutic); the requirement under 35 U.S.C. §101 is only that the claimed composition have **some** use.

With respect to the objection to claims 13 and 28, the Examiner's comments are not understood. However, the term "comprises" has been replaced with "has".

The Examiner's comments with regard to claim 14 is not understood; clarification is respectfully requested.

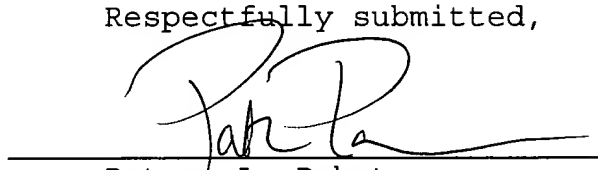
Claim 31 has been amended to correct the antecedent basis.

Claims 32 and 33 have been amended to respond to the Examiner's objections.

All claims as now pending are attached in an Aappendix for the Examiner's convenience.

Examination and reconsideration of all claims 1-32 and 34, as amended, is earnestly solicited.

Respectfully submitted,



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Appendix

1. (amended) An analog of a protein regulating complement activation having short consensus repeats of amino acid sequence selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H, and [these] <u>those</u> complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein said protein analog is selected from the group consisting of complement regulating proteins containing short consensus repeats derived from a second, different complement regulating protein, complement regulating proteins wherein the short consensus repeats are rearranged, complement regulating proteins having defined amino acid substitutions in the short consensus repeats selected from the group consisting of repeats having binding activity, cofactor activity, and decay accelerating activity, wherein the substitution alters the activity of the naturally occurring complement regulatory protein, and complement regulating proteins consisting of as few as three short consenses repeats, wherein the protein [has complement regulatory activity] <u>binds C3b, C4b or C3b and C4b</u>.

2. The analog of claim 1 wherein the complement regulatory activity is selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, C4b cofactor activity, and decay accelerating activity.

3. The analog of claim 2 wherein the protein is complement receptor one.

4. The analog of claim 2 wherein the protein is decay accelerating factor.

5. The analog of claim 2 wherein the protein is factor H.

6. The analog of claim 2 wherein the C3b binding and cofactor activities of the protein are enhanced by substitutions increasing C4b binding of the protein.

7. The analog of claim 2 wherein the C4b binding and cofactor activities of the protein are enhanced by substitutions increasing C3b binding of the protein.

8. The analog of claim 2 wherein the protein contains a change within a short consensus repeat that corresponds with a change to complement receptor one selected from the group consisting of:

CR1-4 with its first 122 amino acids (SCR1-2) replaced with CR1 amino acids 497-618 (SCR 8-9) and CR1-4(8,9) with deletion of 194-253; substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K, or structurally similar amino acids.

9. The analog of claim 2 wherein the protein contains a change within a short consensus repeat that corresponds with a change to complement receptor one selected from the group consisting of:
79: D; 37,39: Y,D; 92: T; 109-112: N-A-A-H; 109-112, 114-117, 121: N-A-A-H, S-T-K-P...Q; 114-117, 121: N-A-A-H, S-T-K-P...Q; 116: K; 116,117: K-P; 92-94: K...Y; 99,103,106: S...T...I; 109-112: P-T-V-I; 110: T; 111: V; 112: I; 114: D; 115: N; 121: D; 117: T; 1,3: Q...N; 6-9: E-W-L-P; 12-16, 18-21: K-L-K-T-Q...N-A-S-D; 27,29: S...K; 37: S; 44, 47, 49: I...K...S; 52-54, 57, 59: T-G-A...R...R; 78-79, 82: K-G...F; 85, 87: Q...K; 12-16, 18-21: R-P-T-N-L...D-E-R-E; 27,29: Y...N; 35, 64-65, 94: G...R-N...Y, substitutions with structurally similar amino acids, and combinations thereof.

10. The analog of claim 2 wherein the complement regulatory protein is decay accelerating factor wherein one or more substitutions are introduced into the region of the protein corresponding to decay accelerating factor short consensus repeats SCRs 2-3 selected from the group consisting of 180-187: S-T-K-P-P-I-C-Q; 175-178: N-A-A-H; 175-187: S-T-K-P-P-I-C-Q-N-A-A-H; 130: R; 145: D; 77-84: K-L-K-T-Q-T-N-A-S-D; 90-92: S-L-K, substitutions with structurally similar amino acids, and combinations thereof.

11. The analog of claim 1 wherein the complement regulatory protein is factor H comprising sequences conferring on the protein an activity selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, and C4b cofactor activity, wherein the sequences are derived from a protein selected from the group consisting of complement receptor 1, membrane cofactor protein, C4 binding protein, and factor H,.

12. The analog of claim 1 comprising at least one short consensus repeat derived from a different protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H.

13. (amended) The analog of claim 1 wherein the protein [comprises] <u>has</u> C3b cofactor activity, C4b cofactor activity and decay accelerating activity.

14. The analog of claim 1 wherein the protein consists essentially of three short consensus regions and has two complement regulatory activities.

15. The analog of claim 1 further comprising a pharmaceutically acceptable carrier for administration to a patient in need thereof.

16. (amended) A method for making an analog of a protein regulating complement activation having short consensus

repeats of amino acid sequence selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H, and these complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, [wherein said] comprising constructing a DNA sequence encoding a protein analog [is] selected from the group consisting of complement regulating proteins containing short consensus repeats derived from a second, different complement regulating protein, complement regulating proteins wherein the short consensus repeats are rearranged, complement regulating proteins having defined amino acid substitutions in the short consensus repeats selected from the group consisting of repeats having binding activity, cofactor activity, and decay accelerating activity, wherein the substitution alters the activity of the naturally occurring complement regulatory protein, and complement regulating proteins consisting of as few as three short consenses repeats, wherein the protein [has complement regulatory activity] binds C3b, C4b, or C3b and C4b, and expressing the DNA sequence in a suitable host for expression of the protein.

17. The method of claim 16 wherein the complement regulatory activity is selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, C4b cofactor activity, and decay accelerating activity.

18. The method of claim 16 wherein the protein is complement receptor one.

19. The method of claim 16 wherein the protein is decay accelerating factor.

20. The method of claim 16 wherein the protein is factor H.

21. The method of claim 17 wherein the C3b binding and cofactor activities of the protein are enhanced by substitutions increasing C4b binding of the protein.

22. The method of claim 17 wherein the C4b binding and cofactor activities of the protein are enhanced by substitutions increasing C3b binding of the protein.

23. The method of claim 17 wherein the protein contains a change within a short consensus repeat that corresponds with a change to complement receptor one selected from the group consisting of:

CR1-4 with its first 122 amino acids (SCR1-2) replaced with CR1 amino acids 497-618 (SCR 8-9) and CR1-4(8,9) with deletion of 194-253; substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K, or structurally similar amino acids.

24. The method of claim 17 wherein the protein contains a change within a short consensus repeat that corresponds with a change to complement receptor one selected from the group consisting of:
79: D; 37,39: Y,D; 92: T; 109-112: N-A-A-H; 109-112, 114-117, 121: N-A-A-H, S-T-K-P...Q; 114-117, 121: N-A-A-H, S-T-K-P...Q; 116: K; 116,117: K-P; 92-94: K...Y; 99,103,106: S...T...I; 109-112: P-T-V-I; 110: T; 111: V; 112: I; 114: D; 115: N; 121: D; 117: T; 1,3: Q...N; 6-9: E-W-L-P; 12-16, 18-21: K-L-K-T-Q...N-A-S-D; 27,29: S...K; 37: S; 44, 47, 49: I...K...S; 52-54, 57, 59: T-G-A...R...R; 78-79, 82: K-G...F; 85, 87: Q...K; 12-16, 18-21: R-P-T-N-L...D-E-R-E; 27,29: Y...N; 35, 64-65, 94: G...R-N...Y, substitutions with structurally similar amino acids, and combinations thereof.

25. The method of claim 17 wherein the complement regulatory protein is decay accelerating factor wherein one or more substitutions are introduced into the region of the protein corresponding to decay accelerating factor short consensus repeats SCRs 2-3 selected from the group consisting of 180-187: S-T-K-P-P-I-C-Q; 175-178: N-A-A-H; 175-187: S-T-K-P-P-I-C-Q-N-A-A-H; 130: R; 145: D; 77-84: K-L-K-T-Q-T-N-A-S-D; 90-92: S-L-K, substitutions with structurally similar amino acids, and combinations thereof.

26. The method of claim 16 wherein the complement regulatory protein is factor H comprising sequences conferring on the protein an activity selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, and C4b cofactor activity, wherein the sequences are derived from a protein selected from the group consisting of complement receptor 1, membrane cofactor protein, C4 binding protein, and factor H.

27. The method of claim 16 comprising at least one short consensus repeat derived from a different protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H.

28. (amended) The method of claim 16 wherein the protein [comprises] <u>has</u> C3b cofactor activity, C4b cofactor activity and decay accelerating activity.

29. The method of claim 16 wherein the protein consists essentially of three short consensus regions and has two complement regulatory activities.

30. The method of claim 16 further comprising mixing with the analog a pharmaceutically acceptable carrier for administration to a patient in need thereof.

31. (amended) A DNA sequence which encodes [the analogs] <u>an analog</u> of claim 1.

32. (amended) The DNA sequence of claim 31 [in] inserted into an expression [system] vector operably linked to control sequences compatible with a compatible host which is capable, when transformed into [a compatible recombinant] the host cell, of expressing a DNA encoding [the] an analog of claim 1[; the expression system comprising a DNA encoding the analog operably linked to control sequences compatible with the host].

Please cancel claim 33.

34. (amended) A method for enhancing the C4b or C3b cofactor activity of a complement regulatory protein, wherein the protein has either C3b or C4b cofactor activity, comprising adding sequences to the protein conferring binding of the other ligand, either C4b or C3b.